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# Synthesis and Antimicrobial Screening of Some New Thiazole Substituted 1,3,4-oxadiazole Derivatives †

**Siddhant V. Kokate [1] and Sachin V. Patil [2,*]**

[1] Department of Química DCNE, Campus Guanajuato, Universidad de Guanajuato, Guanajuato 36050, Mexico; siddhantkokate@gmail.com
[2] Department of Chemistry, HPT Arts and RYK Science College, Nashik 422005, India
* Correspondence: sachin.dhokare@yahoo.com
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**Abstract:** In the present work the synthesis and antimicrobial activity of new thiazole substituted 1,3,4-oxadiazole derivatives was achieved. The reaction of different thioamides with ethyl 4-chloro-3-oxobutanoate (4-chloro ethyl acetoacetate) gave ethyl 2(2-arylthiazol-4yl)acetate**,** which on subsequent reaction with hydrazine hydrate in absolute ethanol afforded 2-(2-arylthiazol-4-yl)acetohydrazide. 2-(2-arylthiazol-4-yl) acetohydrazide on reaction with $CS_2$ and KOH in aqueous ethanol cyclized to form 5-((2-arylthiazol-4-yl)methyl)-1,3,4-oxadiazole-2-thiol. Finally, 5-((2-arylthiazol-4-yl) methyl)-1,3,4-oxadiazole-2-thiol were further treated with $\alpha$-halo ketones at room temperature to afford the target compounds**.** Most of the compounds showed good antibacterial as well as antifungal activity.

**Keywords:** thiazole substituted 1,3,4-oxadiazole derivatives; thioamides; ethyl 4-chloro-3-oxobutanoate; $\alpha$-halo ketones; antibacterial and antifungal activity

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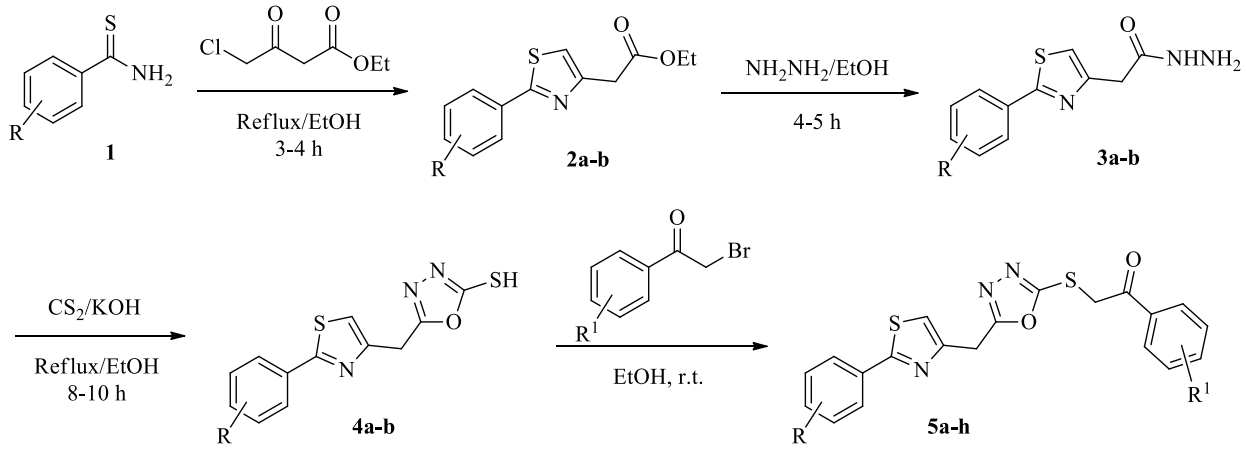
## 1. Introduction

It is observed from literature that thiazole heterocycle is an important moiety and it has been detected that numerous remarkable biological activities are accompanying with thiazole derivatives. Large uses of thiazole were originate in drug progress for the treatment of allergies [1], inflammation [2], HIV infections [3] and more recently for the treatment of pain [4], and as new inhibitors of bacterial DNA gyrase B [5], antitumor [6], antibiotic [7–10], anti-inflammatory [11], antibacterial and antifungal [12,13] antitubercular [14–16] antiviral [17] and Peroxisome proliferator-activated receptor (PPAR) $\alpha/\gamma/\delta$ pan agonists [18].

Furthermore, thiazoles heterocycles are noteworthy class of heterocyclic compounds which is present in several important biologically dynamic drug molecules like Ritonavir as antiretroviral drug, Sulfathiazole as antimicrobial drug, Tiazofurin as antineoplastic drug, and Abafungin as an antifungal drug [19]. Thiazole containing heterocycles showed various biological activities like antihypertensive, antimicrobial and antifungal, anti-HIV, anticonvulsant and anti-inflammatory activities [20–24]. Derivatives of thiazole are also well-known to possess anticancer activities [25–27]. Thiazole derivatives showed anti-inflammatory [28,29], antibacterial [30], antihypertensive [31], antituberculosis [32], analgesic [33] and anticonvulsant activities [34].

Literature search revealed that oxadiazole heterocycle clubbed with thiazole showed different biological activities like antimicrobial, antitumor, and antifungal activities [35–38], stearyl-CoA desaturase inhibition activity [39], antimicrobial and antitubercular activity [40,41], anti-proliferative, anti-mitotic, and microtubule destabilizing activities [42], antitumor activity [43] and anti-micobacterial activity [44,45]. Above results encouraged us to plan new thiazol containing 1,3,4-oxadiazole derivatives and monitor for

antibacterial and antifungal activity. In the present work, we report the synthesis and antimicrobial activity of new thiazole substituted 1,3,4-oxadiazole derivatives.




| Compound | 5a | 5b | 5c | 5d | 5e | 5f | 5g | 5h |
|---|---|---|---|---|---|---|---|---|
| **R** | H | H | H | H | 4-Cl | 4-Cl | 4-Cl | 4-Cl |
| **R¹** | 4-F | 4-Cl | 4-Br | H | 4-F | 4-Cl | 4-Br | H |

**Scheme 1.** Synthetic route of **5a-h**.

## 2. Results and Discussion

The structure of ethyl-2(2-arylthiazol-4yl) acetate **2a-b** was confirmed by the appearance of band at 1725–30 $cm^{-1}$ due to C=O stretching of ester functional group. The structures of compounds **3a-b** was confirmed by absorption bands in region of 3180–3320 $cm^{-1}$, 1680–1690 $cm^{-1}$ due to C=O and $NHNH_2$. Cyclization reaction of compounds **3a-b** with $CS_2$ in presence of KOH to form 1,3,4-oxadiazoles **4a-b** was confirmed by the disappearance of band at 3180–3320 $cm^{-1}$ and 1680–1690 $cm^{-1}$ and appearance of new band at 2450–2510 $cm^{-1}$ due to SH stretching. The structures of **4a-b** was also confirmed by $^1H$ NMR spectra which showed broad singlet at 11 ppm due to SH, singlet at 7.1–7.2 ppm due to thiazolyl proton, singlet at 4.4–4.5 ppm due to $CH_2$ and multiplet at 7.4–8.2 ppm due to aromatic protons. Conversion of **4a-b** to the target compounds **5a-h** was also confirmed by elemental analysis, IR, $^1H$ NMR, $^{13}C$ NMR and MS. The IR spectra of these compounds showed bands at 1690–1700 $cm^{-1}$ due to C=O. The $^1H$ NMR spectra of compounds **5a-h** showed two singlets at 4.4–4.5 ppm and 4.8–4.9 ppm due to two $CH_2$ groups, one singlet in the region of 7.1–7.2 ppm due to thiazolyl proton while the aromatic protons appeared as multiplet at 7.4–8.2 ppm. The molecular ion peaks of all title compounds were obtained from EI-MS. The presence of M+2 peaks were characteristic for the compounds with chlorine and bromine atoms.

## 3. Biological Results and Discussion

All the synthesized compounds were screened for their antibacterial and antifungal activities. Most of the compounds **5a-h** showed good antibacterial as well as antifungal activity as shown in Table 1. The antimicrobial activity results clearly indicated that S-substituted thiazolyl-1,3,4-oxadiazole derivatives **5a-h** showed enhanced antimicrobial activity as compared to thiazolyl oxadiazole compound **4a** and **4b** in which the SH group is free. It was further observed that in compounds **5a** and **5e** in which $R^1$ is 4-F substituted showed good antibacterial as well as antifungal activity irrespective of the R group.

**Table 1.** Antimicrobial screening of synthesized compounds.

| Compd. | *S. aureus* | *E. coli* | *B. subtilis* | *P. aeruginosa* | *A. niger* | *C. albicans* |
|---|---|---|---|---|---|---|
| **4a** | 11.5 | 10 | - | 9.6 | 9.65 | 12.5 |
| **4b** | 10.9 | 8.85 | 9.12 | - | 8.9 | 11.6 |
| **5a** | 20 | 19 | - | 13.1 | 12.54 | 14 |
| **5b** | 17.8 | - | - | 12 | - | 12.5 |
| **5c** | 15.4 | 16.1 | - | 10.5 | 9.4 | 12 |
| **5d** | 14.6 | 14.8 | - | 10 | 9 | 11.5 |
| **5e** | 21.5 | - | 18.3 | - | 14.51 | 16.5 |
| **5f** | 18.5 | 17.5 | 15.4 | - | - | 14.7 |
| **5g** | - | 16 | 15 | - | 11.6 | - |
| **5h** | 15.3 | 14.8 | 14.6 | - | 10.3 | 12.4 |
| **Nystatin** | NA | NA | NA | NA | 21.12 | 21.96 |
| **Chloramphenicol** | 32.8 | 29.14 | 30.11 | 24.68 | NA | NA |

Zone diameter of growth inhibition in mm calculated by digital vernier Caliper. NA-not applicable; (-) = inactive. Chloramphenicol (100 μg/disc) and Nystatin (100 μg/disc) were used as reference; synthesized compounds (100 μg/disc).

## 4. Experimental

*General procedure for synthesis of 3a-b: synthesized as per reference no. 38.*

*General procedure for the synthesis of 5-((2-arylthiazol-4-yl)methyl)-1,3,4-oxadiazole-2-thiol* (**4a-b**)

To a mixture of compound **3** (1 mmol) in ethanol (25 mL), carbon disulphide (1.3 mmol) and potassium hydroxide (1 mmol) was added. The reaction mixture was refluxed gently on water bath till evolution of $H_2S$ ceased. Progress of the reaction was monitored by TLC (30% Ethyl acetate/hexanes). After completion of the reaction the solvent was completely removed, the residue was poured in water and acidified with conc. HCl to obtain solid product which was filtered, dried and recrystallized from ethanol.

**Table 2.** Physical data of compounds **4a-b**.

| Compound | Colour | M.P. (°C) | $R_f$ Value/ Solvent System (Ethyl Acetate/Hexane:s | Yield (%) |
|---|---|---|---|---|
| **4a** | Grey | 184–186 | 0.12/7:3 | 71 |
| **4b** | Grey | 218–220 | 0.13/7:3 | 75 |

*General procedure for the synthesis of 2-(5-(2-arylthiazol-4-yl)methyl)2-thiosubstituted-1,3,4-oxadiazole derivatives (**5a-h**)*

To a stirred solution of compound **4a-b** (1 mmol) in Ethanol, substituted *α*-haloketones (1 mmol) was added. The reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC (30% Ethyl acetate/hexanes). After completion, the reaction mixture was poured in crushed ice to obtain solid product which was filtered, dried and purified by column chromatography on silica gel using 2% of ethyl acetate/hexanes.

## 5. Spectral Data

*2-(5-((2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-fluorophenyl) ethanone* (**5a**) Yield: (68%); mp: 99–103 °C; IR (KBr, $cm^{-1}$): 3120, 2931, 2854, 1690, 933 785, 688; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.4–7.6 (m, 5H, Ar-H), 7.1 (s, 1H, thiazolyl-H), 4.4 (s, 2H, $CH_2$), 4.8 (s, 2H, S-$CH_2$), 8.1 (d, J = 8.2 Hz, 2H, Ar-H), 7.2 (dd, J = 11.5 and 8.2 Hz, 2H, Ar-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 128.8, 129.0, 127.0, 132.0, 169.0, 109.0, 150.0, 32.0, 165.0, 169.0,

35.0, 183.0, 132.0, 130.0, [115.5, 115.8(d, J = 22.5 Hz, 2C)], [165.3, 162.1(d, J = 243 Hz, 1C)]; Anal. Calcd for $C_{20}H_{14}FN_3O_2S_2$: C, 58.38; H, 3.43; N, 10.21; Found: C, 58.24; H, 3.28; N, 10.42; MS (EI, 70 eV): *m*/*z* (%) 411 ($M^+$), 412(M+1).

*2-(5-((2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-chlorophenyl) ethanone* (**5b**) Yield: (65%); mp: 105–108 °C; IR (KBr, $cm^{-1}$): 3118, 2930, 1690, 938, 688; $^1H$ NMR ($CDCl_3$, 300MHz): δ 7.4–7.6(m, 5H, Ar-H), 7.1(s, 1H, thiazolyl-H), 4.4(s, 2H, $CH_2$), 4.8(s, 2H, S-$CH_2$), 7.7(d, J = 8.4 Hz, 2H, Ar-H), 7.9(d, J = 8.4, 2H, Ar-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 128.8, 129.0(2C), 127.0(2C), 132.0, 169.0, 109.0, 150.0, 32.0, 165.0, 169.0, 35.0, 183.0, 137.0, 130.0(2C), 131.0(2C), 136.3; Anal. Calcd for $C_{20}H_{14}ClN_3O_2S_2$: C, 56.13; H, 3.30; N, 9.82; Found: C, 56.21; H, 3.28; N, 9.71; MS (EI, 70 eV): *m*/*z* (%) 427 ($M^+$), 428(M+1).

*2-(5-((2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-bromophenyl) ethanone* (**5c**) Yield: (70%); mp: 110–116 °C; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.4–7.6(m, 5H, Ar-H), 7.1(s, 1H, thiazolyl-H), 4.4(s, 2H, $CH_2$), 4.8(s, 2H, S-$CH_2$), 7.9(d, J = 8.3 Hz, 2H, Ar-H), 7.6(d, J = 8.3Hz, 2H, Ar-H); Anal. Calcd for $C_{20}H_{14}BrN_3O_2S_2$: C, 50.58; H, 2.99; N, 8.90; Found: C, 50.49; H, 3.11; N, 8.85; MS (EI, 70 eV): *m*/*z* (%) 471 ($M^+$), 472(M+1).

*2-(5-((2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-phenylethanone* (**5d**) Yield: (72%); mp: 100–106 °C; IR (KBr, $cm^{-1}$): 3120, 2931, 1690, 785, 688; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.4–7.9(m, 10H, Ar-H), 7.1(s, 1H, thiazolyl-H), 4.4(s, 2H, $CH_2$), 4.8(s, 2H, S-$CH_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 128.8, 129.0(2C), 127.0(2C), 132.0, 169.0, 109.0, 150.0. 32.0, 165.0, 169.0, 35.0, 183.0, 135.0, 131.0(2C), 131.5(2C), 129.3; Anal. Calcd for $C_{20}H_{15}N_3O_2S_2$: C, 61.05; H, 3.84; N, 10.68; Found: C, 61.14; H, 3.74; N, 10.56; MS (EI, 70 eV): *m*/*z* (%) 393 ($M^+$), 394(M+1).

*2-(5-((2-(4-chlorophenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-fluoro phenyl)ethanone* (**5e**) Yield: (69%); mp: 115–118 °C; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.4(d, J = 8.3Hz, 2H, Ar-H), 7.5(d, J = 8.3Hz, 2H, Ar-H), 7.2(s, 1H, thiazolyl-H), 4.4(s, 2H, $CH_2$), 4.8(s, 2H, S-$CH_2$), 8.1(d, J = 8.4 Hz, 2H, Ar-H), 7.3(dd, J = 11.2 and 8.3Hz, 2H, Ar-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 134.2, 128.7(2C), 128.3(2C), 131.0, 170.1, 109.4, 150.1, 32.0($CH_2$), 166.4, 170.2, 35.0(S-$CH_2$), 183.1(C=O), 132.0, 130.0(2C), [116.2, 115.9(d, J = 22.5 Hz, 2C)], [164.4, 161.2(d, J = 244 Hz, 1C)]; Anal. Calcd for $C_{20}H_{13}ClFN_3O_2S_2$: C, 53.87; H, 2.94; N, 9.42; Found: C, 53.79; H, 2.79; N, 9.34. MS (EI, 70 eV): *m*/*z* (%) 445($M^+$), 446(M+1).

*2-(5-((2-(4-chlorophenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-clororophenyl) ethanone* (**5f**) Yield: (64%); mp: 112–116 °C; IR (KBr, $cm^{-1}$): 3090, 2950, 1690, 2835, 964, 802, 765; $^1H$ NMR ($CDCl_3$, 300MHz): δ 7.4(d, J = 8.3Hz, 2H, Ar-H), 7.5(d, J = 8.3Hz, 2H, Ar-H), 7.2(s, 1H, thiazolyl-H), 4.4(s, 2H, $CH_2$), 4.8(s, 2H, S-$CH_2$), 7.8(d, J = 8.3 Hz, 2H, Ar-H), 7.9(d, J = 8.3Hz, 2H, Ar-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 134.2, 128.7(2C), 128.3(2C), 131.0, 170.1, 109.4, 150.1, 32.0($CH_2$), 166.4, 170.2, 35.0(S-$CH_2$), 183.1(C=O), 135.7, 130.0(2C), 130.8(2C), 136.7; Anal. Calcd for $C_{20}H_{13}Cl_2N_3O_2S_2$: C, 51.95; H, 2.83; N, 9.09; Found: C, 52.08; H, 2.76; N, 9.18. MS (EI, 70 eV): *m*/*z* (%) 461($M^+$), 462(M+1).

*2-(5-((2-(4-chlorophenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-bromo phenyl) ethanone* (**5g**) Yield: (71%); mp: 101–105 °C; $^1H$ NMR ($CDCl_3$, 300MHz): δ 7.4(d, J = 8.3Hz, 2H, Ar-H), 7.5(d, J = 8.3Hz, 2H, Ar-H), 7.2(s, 1H, thiazolyl-H), 4.4(s, 2H, $CH_2$), 4.8(s, 2H, S-$CH_2$), 7.8(d, J = 8.1Hz, 2H, Ar-H), 7.6(d, J = 8.1Hz, 2H, Ar-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 134.2, 128.3(2C), 128.5(2C), 131.0, 170.0, 109.4, 150.1, 32.0($CH_2$), 166.4, 170.2, 35.0(S-$CH_2$), 183.1(C=O), 135.5, 131.0(2C), 131.5(2C), 128.0; Anal. Calcd for $C_{20}H_{13}BrClN_3O_2S_2$: C, 47.40; H, 2.59; N, 8.29; Found: C, 47.31; H, 5.57; N, 8.92. MS (EI, 70 eV): *m*/*z* (%) 505($M^+$), 506(M+1).

*2-(5-((2-(4-chlorophenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-phenyl ethanone* (**5h**) Yield: (69%); mp: 121–125 °C; IR (KBr, $cm^{-1}$): 3120, 2930, 1690, 933, 785, 688; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.4(d, J = 8.3Hz, 2H, Ar-H), 7.5(d, J = 8.3Hz, 2H, Ar-H), 7.2(s, 1H, thiazolyl-H), 4.4(s, 2H, $CH_2$), 4.8(s, 2H, S-$CH_2$), 7.6–7.8(m, 5H, Ar-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 134.2, 128.5(2C), 128.2(2C), 131.1, 170.1, 109.5, 150.1, 32.2($CH_2$), 166..0, 170.2, 35.0(S-$CH_2$), 183.1(C=O), 135.8, 128.7(2C), 128.5(2C), 129.2; Anal. Calcd for $C_{20}H_{14}ClN_3O_2S_2$: C, 56.13; H, 3.30; N, 9.82; Found: C, 56.27; H, 3.21; N, 9.78. MS (EI, 70 eV): *m*/*z* (%) 427($M^+$), 428(M+1).

## 6. Conclusion

Different S-substituted 1,3,4-oxadiazole derivatives were synthesized and evaluated for their antimicrobial activities. It was interesting to note that compounds with S-substitution were found to be biologically more potent as compared to their respective unsubstituted derivatives. Therefore, our assumption that antimicrobial activity could be modified by incorporating more than one heterocyclic nuclei in the same molecule could possibly lead us derivatives with enhanced activity. These molecules thus could act as lead molecules for further exploration of new drug molecules.

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